Sleep Medicine 15 (2014) 1212–1218

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep-related intermittent hypoxemia and glucose intolerance: a community-based study

Sakurako Tanno [a,b], Takeshi Tanigawa [a,*], Isao Saito [c], Wataru Nishida [d], Koutatsu Maruyama [e], Eri Eguchi [a], Susumu Sakurai [f], Haruhiko Osawa [d], Naresh M. Punjabi [g]

[a] Department of Public Health, Ehime University Graduate School of Medicine, Toon, Japan
[b] Center of Sleep Medicine, Ehime University Hospital, Toon, Japan
[c] Department of Basic Nursing and Health Science, Ehime University Graduate School of Medicine, Toon, Japan
[d] Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine, Toon, Japan
[e] Department of Basic Medical Research and Education, Ehime University Graduate School of Medicine, Toon, Japan
[f] Department of Clinical Laboratory Science, Faculty of Health Care, Tenri Health Care University, Tenri, Japan
[g] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 7 November 2013
Received in revised form 23 April 2014
Accepted 29 May 2014
Available online 27 June 2014

Keywords:
Sleep-disordered breathing
Sleep apnea
Diabetes mellitus
Impaired glucose tolerance
Epidemiology
Oximetry
Oral glucose tolerance test

ABSTRACT

Background: Intermittent hypoxemia is a fundamental pathophysiological consequence of sleep-disordered breathing and may alter glucose metabolism. To characterize the association between sleep-related intermittent hypoxemia and glucose metabolism, overnight pulse-oximetry and an oral glucose tolerance test were completed in a cohort of middle-aged and older Japanese adults.
Methods: The study sample consisted of 1836 community-dwelling Japanese (age, 30–79 years; women, 65.5%; mean body mass index, 23.1 kg/m^2). The oxygen desaturation index (ODI) was quantified during sleep using a ≥3% oxygen desaturation threshold and categorized as normal (<5.0 events/h), mild (5.0–15.0 events/h), and moderate to severe (≥15.0 events/h). The independent associations between the ODI and the prevalence of impaired fasting glucose, impaired glucose tolerance, diabetes, and two metrics of insulin resistance [homeostasis model assessment index for insulin resistance (HOMA-IR) and Matsuda index] were examined.
Results: Compared with subjects with an ODI < 5 events/h, the adjusted odds ratio for prevalent impaired fasting glucose, glucose intolerance, and diabetes for subjects with an ODI ≥15.0 events/h were 1.27 (95% confidence interval, 0.72–2.23), 1.69 (1.03–2.76), and 1.28 (0.59–2.79), respectively. Both HOMA-IR and Matsuda index were significantly associated with the severity of sleep-related intermittent hypoxemia as assessed by the ODI (P for trend = 0.03 and 0.007, respectively).
Conclusion: Among middle-aged and older Japanese adults, sleep-related intermittent hypoxemia is associated with glucose intolerance and insulin resistance, and may contribute to the development of type 2 diabetes mellitus.

1. Introduction

The International Diabetes Federation estimates that ~366 million people worldwide had type 2 diabetes mellitus in 2011 [1]. It is projected that, by the year 2030, the prevalence of type 2 diabetes will continue to rise in epidemic proportions and affect 552 million people globally [1]. Over the last decade, a large body of empirical evidence has accumulated indicating that sleep-disordered breathing (SDB) is independently associated with insulin resistance, glucose intolerance, and type 2 diabetes [2,3]. Experimental data from animal and human studies indicate that intermittent hypoxemia and recurrent arousals in SDB may predispose to the development of metabolic abnormalities [4–7] by increasing sympathetic neural traffic [8] and oxidative stress [9]. Although the risk of type 2 diabetes varies across ethnic groups [10], most previous studies on SDB and metabolic dysfunction have primarily included subjects of Caucasian descent. Examining whether SDB is associated with alterations in glucose metabolism in Asian samples is of clinical and public health value, especially given the high prevalence of metabolic abnormalities in these populations [11]. Thus, the current study sought to examine the association between SDB and glucose metabolism in an Asian sample of middle-aged and older men and women. It was

* Corresponding author at: Department of Public Health, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan. Tel.: +81 89 960 5281; fax: +81 89 960 5284.
E-mail address: tt9178tt9178@gmail.com (T. Tanigawa).

http://dx.doi.org/10.1016/j.sleep.2014.05.027
1389-9457/

hypothesized that the severity of sleep-related intermittent hypoxemia would be independently associated with insulin resistance and glucose intolerance, similar to what has been previously demonstrated in subjects of Caucasian descent. The current study also assessed whether severity of sleep-related hypoxemia correlates with static and dynamic measures of glucose metabolism in an Asian sample.

2. Methods

2.1. Study population

The study sample for the current investigation was derived from the Toon Health Study, which is a prospective cohort study in Toon City, Ehime prefecture of Japan. The cohort study was initiated in 2009 to characterize the risk factors for cardiovascular disease in a community setting. Toon City is a rural area located in the southern part of Japan with a population of ~35,000. Participants residing in the city and responding to newspaper advertisements, posters, or invitations were considered eligible if they were 30–79 years in age. In all, 2033 participants (726 men and 1307 women) enrolled from 2009 to 2012. Those receiving treatment for SDB ($n = 7$) or type 2 diabetes mellitus ($n = 73$) at the time of the survey were excluded from the current analyses. Participants with incomplete data on overnight oximetry ($n = 74$) or without data on the oral glucose tolerance test (OGTT) were also excluded ($n = 43$). Participants were excluded from OGTT if they were currently receiving treatment for diabetes mellitus or had a prior history of total gastrectomy. Those using corticosteroids or with a family history of diabetes mellitus had their fasting blood glucose level measured by a portable glucose monitor; if the fasting blood glucose level was ≥140 mg/dL, they were excluded from the OGTT. Of the 102 participants who did not undergo the OGTT, seven had a fasting blood glucose ≥140 mg/dL.

Prevalent medical conditions associated with SDB were assessed for the study cohort. Among the 1836 participants included in the final analysis, 814 women were postmenopausal, 81 participants had history of angina pectoris, 13 had a history of myocardial infarction, 22 had history of arrhythmia including atrial fibrillation, 28 had a history of stroke, 22 had a history of pulmonary conditions including asthma and emphysema, and three had a history of miscellaneous heart disease. The study protocol was approved by the Institutional Review Board of Ehime University Graduate School of Medicine and informed consent was obtained from each study participant.

2.2. Assessment of sleep-disordered breathing

Study participants were monitored overnight with pulse oximetry (PULSOX-3Si; Konica Minolta Co., Osaka, Japan). The portable sleep monitor was placed on the left wrist for one night of monitoring during sleep at home. The oximetry sensor from the portable monitor was placed on the fourth finger and secured with removable tape. Oximetry data were downloaded to a desktop computer via an interface (PULSOX IF-3; Konica Minolta) and subjected to a computerized algorithm to identify oxygen desaturations of ≥3%. The oxygen desaturation event index (ODI), average oxygen saturation, and minimum oxygen saturation were determined. The following two thresholds were used to define the ODI: ≥3% and ≥4%. To avoid erroneous minimum oxygen saturation values, each oximetry tracing was reviewed by trained staff to remove potential artifacts and to verify the minimum oxygen saturation value reported. Because the duration of nocturnal sleep was not directly recorded, each subject was instructed to complete a sleep diary and provide an estimate of sleep duration. In the sleep diary, participants reported their bed and wake-up times. Awakenings during the night were also reported in the nightly diary. During the review of the oximetry tracings, information from the sleep diary was reviewed to verify the self-reported time in bed. Based on the ODI and defined using the ≥3% threshold, severity of SDB was determined as follows: normal (<5 event/h), mild disease (5.0–14.9 events/h) and moderate to severe (≥15.0 events/h).

2.3. Oral glucose tolerance test

All participants were required to fast for ≥10 h before the OGTT. Venous blood samples were obtained at baseline, 60 min, and 120 min after the ingestion of 75 g of a glucose solution (Toleran G, Ajinomoto, Tokyo, Japan). The homeostasis model assessment index for insulin resistance [HOMA-IR; fasting plasma insulin (FPI) (μIU/mL) × fasting plasma glucose (FPG) (mg/dL)/405] was used as an index of insulin resistance [12]. In addition, the Matsuda index {10,000/√[FPG × FPI × (mean PG × mean PI)]}, which is highly correlated with the euglycemic insulin-clamp-derived insulin sensitivity [13], was determined to approximate hepatic and muscle insulin sensitivity. Finally, pancreatic beta-cell function was assessed using the HOMA-B {360 × FPI (μIU/mL)/[FPG (mg/dL) – 63]} [12]. Based on the recommendations by the American Diabetes Association [14], impaired fasting glucose was defined as values between 100 and 125 mg/dL. Glucose intolerance was defined as 2 h glucose values between 140 and 199 mg/dL and diabetes mellitus as fasting glucose values ≥126 mg/dL or as 2 h serum glucose values after the glucose challenge ≥200 mg/dL, or both. Serum insulin was measured by electrochemiluminescence immunoassay (Roche Diagnostics K.K., Tokyo, Japan).

2.4. Assessment of covariates

Several covariates that could confound the association between SDB and glucose metabolism were assessed. Trained nutritionists interviewed each participant on health habits including daily alcohol intake, smoking, physical activity, and average sleep duration. Usual weekly alcohol intake was determined in grams of ethanol consumed per day. As a metric of physical activity, total energy expenditure (TEE) was assessed using the Japan Arteriosclerosis Longitudinal Study Physical Activity Questionnaire (JALSPAQ) [15]. Participants were queried on other prevalent medical conditions by physicians. Height and weight were measured in light clothing to calculate body mass index (BMI). Waist circumference was measured at the level of the umbilicus in the standing position.

2.5. Statistical analysis

Age and sex-adjusted values for BMI (kg/m^2), ethanol intake, TEE, current smoking, exercise, sleep duration and outcomes of OGTT were calculated and compared across the three categories of SDB severity (<5.0, 5.0–14.9, and ≥15.0 events/h) using analysis of covariance (ANCOVA) and the χ^2-test. Multiple logistic regression analyses were used to assess the independent association between SDB severity (i.e. ODI categories) and glycemic status. The average and minimum oxygen saturation values were also categorized into quartiles for additional multivariable modeling. The prevalent odds ratio for impaired fasting glucose, glucose intolerance, and diabetic glucose tolerance were determined for categories of SDB severity after adjusting for age, sex, BMI, ethanol intake per day (<20, 20–40, 40–60, ≥60 g), current smoking (yes/no), exercise more than two times per week (yes/no), TEE (kcal/kg/d), and sleep duration (h/d). Linear trends were examined using multiple logistic regression models that incorporated the median values of ODI categories or oxygen saturation categories. Multivariable adjusted mean values of HOMA-IR, Matsuda index, and HOMA-B were also determined using the ANCOVA technique with $ODI_{3\%}$ or average saturation as the main effect. Linear trends were assessed with the ANCOVA

Table 1
Age- and sex-adjusted means and prevalences of risk factors according to 3% ODI levels.

	SDB severity (ODI, events/h)			*P* for trend
	<5.0 (*n* = 1307)	5.0–14.9 (*n* = 418)	≥15 (*n* = 111)	
Age (years)	55.0	63.1	63.9	<0.0001
Male sex (%)	27.6	45.1	74.9	<0.0001
Body mass index (kg/m^2)	22.5	24.2	25.2	<0.0001
Waist circumference (cm)	81.9	85.7	88.3	<0.0001
Ethanol intake (g/d)	7.93	8.06	13.4	0.004
Current smoking (%)	7.80	14.9	14.3	0.96
Exercise ≥2 times per week (%)	39.4	35.1	33.8	0.12
Total energy expenditure (kcal/kg/d)	35.5	35.2	34.0	<0.001
Sleep duration (h/d)	6.50	6.43	6.56	0.90
Oxygen desaturation index (/h)				
3%	1.86	8.23	22.9	<0.001
4%	0.93	5.18	17.7	<0.001
Oxygen saturation (%)				
Average	96.7	96.1	95.3	<0.001
Minimum	90.6	84.8	80.9	<0.001
Serum glucose (mg/dL)				
Fasting	91.8	92.6	94.0	0.01
1 h	141.9	150.9	153.9	<0.001
2 h	119.7	124.6	131.7	<0.001
Serum insulin (μU/mL)				
Fasting	4.57	5.52	6.56	<0.0001
1 h	44.8	52.1	55.9	<0.0001
2 h	38.3	46.4	55.8	<0.0001
HOMA-IR	1.03	1.26	1.52	<0.0001
Matsuda index	7.45	6.09	5.17	<0.0001
HOMA-B	59.2	69.5	79.0	<0.0001

Abbreviations: ODI, oxygen desaturation index; SDB, sleep-disordered breathing; HOMA-IR, homeostasis model assessment index for insulin resistance; HOMA-B, homeostasis model assessment index for pancreatic beta-cell function.

technique using the median values of $ODI_{3\%}$ categories or average saturation categories. Effect modification by sex or BMI were tested separately by inclusion of an interaction term of either sex or BMI (<25 and ≥25 kg/m^2) by median values of ODI categories. All statistical analyses were performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA). All *P*-values are two-tailed and $P < 0.05$ was regarded as statistically significant.

3. Results

The study sample consisted of 1836 participants (633 men and 1203 women). Table 1 shows the age and sex-adjusted means and percentages of cardiovascular risk factors across the three ODI categories. BMI, waist circumference, alcohol intake, serum glucose and insulin values, HOMA-IR and HOMA-B were positively associated with SDB severity. In contrast, physical activity and Matsuda index of insulin sensitivity were negatively associated with increasing severity of SDB.

Table 2 displays the age- and sex-adjusted and multivariable-adjusted odds ratios for prevalent impaired fasting glucose, glucose intolerance, and diabetes as a function of various parameters derived from overnight oximetry. Compared with participants without SDB ($ODI_{3\%} < 5.0$ events/h), the adjusted odds ratio of glucose intolerance for those with moderate-to-severe SDB ($ODI_{3\%} \geq 15.0$ events/h) was 1.69 [95% confidence interval (CI), 1.03–2.76; *P* for trend = 0.04]. In contrast, the prevalence of impaired fasting glucose or diabetes was not significantly associated with $ODI_{3\%}$. Analyses using the ODI based on the 4% desaturation threshold also demonstrated a significant association between glucose intolerance and SDB with an adjusted odds ratio of 1.53 (95% CI, 1.10–2.14) comparing participants with moderate-to-severe SDB ($ODI_{4\%}$ 5.0–14.9 events/h) to those without SDB ($ODI_{4\%} < 5.0$ events/h, *P* for trend = 0.04). Not surprisingly, an association between average oxygen saturation during sleep and glucose intolerance was also observed. Multivariable models incorporating various confounders showed an adjusted odds ratio for glucose intolerance of 1.60 (95% CI, 1.09–2.37) comparing an average oxygen saturation in the range of 88.5% and 95.8% to an average oxygen saturation between 97.2% and 99.5% (*P* for trend = 0.004). Similarly, the adjusted odds ratio for diabetes was 2.12 (95% CI, 1.15–3.19; *P* for trend < 0.001) comparing the two aforementioned categories of average oxygen saturation. Interestingly, the minimum oxygen saturation showed no significant associations with impaired fasting glucose, glucose intolerance, or diabetes.

When sex-stratified analyses were conducted, the association between metrics of SDB and glucose intolerance was not materially significant between men and women. In men, the adjusted odds ratio of glucose intolerance for moderate-to-severe SDB ($ODI_{3\%} \geq 15.0$ events/h) compared with no SDB ($ODI_{3\%} < 5$) was 1.65 (95% CI, 0.87–3.15; *P* for trend = 0.15), whereas in women it was 1.38 (95% CI, 0.59–3.21; *P* for trend = 0.26). Analyses were also undertaken by strata of age (<65 years vs ≥65 years). In the younger group (<65 years), the adjusted odds ratio of glucose intolerance for moderate-to-severe SDB ($ODI_{3\%} \geq 15.0$ events/h) compared with no-SDB was 1.50 (95% CI, 0.74–3.07; *P* for trend = 0.09), whereas in the older group (≥65 years) it was 2.65 (95% CI, 1.32–5.32; *P* for trend = 0.007). Sensitivity analyses that included participants treated for diabetes or those who did not complete the OGTT but had a fasting glucose ≥126 mg/dL showed that the adjusted odds ratio of diabetes for those with moderate-to-severe SDB ($ODI_{3\%} \geq 15.0$ events/h) was 1.36 (0.73–2.54), compared with those without SDB (*P* for trend = 0.32). Participants with an average oxygen saturation between 88.5% and 95.8% had an adjusted odds ratio for diabetes of 1.66 (1.01–2.73; *P* for trend = 0.002) when compared with participants with an average oxygen saturation between 97.2% and 99.5%.

Figure 1 shows multivariable-adjusted means for HOMA-IR Matsuda index, and HOMA-B as a function of SDB severity. Both HOMA-IR and Matsuda index were significantly associated with $ODI_{3\%}$ and the average oxygen saturation (*P* for trend = 0.03 and 0.07, respectively). HOMA-B also showed a positive but marginally significant association with $ODI_{3\%}$ (*P* for trend = 0.051). Similarly,

Table 2
Sex-, age-, and multivariable-adjusted odds ratios of IFG, IGT, and DM as a function of oxygen desaturation index (3% and 4%), average oxygen saturation, and minimum oxygen saturation.

Model/variable	*N*	IFG (*n* = 248) OR (95% CI)	IGT (*n* = 377) OR (95% CI)	DM (*n* = 119) OR (95% CI)
Model 1 (adjusted for age and sex)				
3% ODI				
<5.0	1307	1.00	1.00	1.00
5.0–14.9	418	1.13 (0.80–1.59)	1.31 (0.98–1.75)	1.21 (0.77–1.90)
≥15.0	111	1.90 (1.11–3.25)	2.34 (1.46–3.75)	1.79 (0.86–3.73)
P for trend		0.02	<0.001	0.11
4% ODI				
<5.0	1528	1.00	1.00	1.00
5.0–14.9	251	1.45 (0.98–2.13)	1.74 (1.26–2.41)	1.41 (0.85–2.35)
≥15.0	56	1.84 (0.94–3.59)	2.11 (1.14–3.87)	0.67 (0.19–2.37)
P for trend		0.02	<0.001	0.86
Average oxygen saturation				
97.2–99.5%	443	1.00	1.00	1.00
96.6–97.2%	458	1.14 (0.73–1.80)	1.11 (0.76–1.61)	0.72 (0.36–1.47)
95.8–96.6%	468	1.59 (1.03–2.45)	1.64 (1.14–2.35)	1.42 (0.77–2.62)
88.5–95.8%	465	2.06 (1.34–3.18)	2.18 (1.52–3.15)	2.65 (1.50–4.70)
P for trend		<0.001	<0.001	<0.001
Minimum oxygen saturation				
93–98%	416	1.00	1.00	1.00
90–92%	452	1.09 (0.69–1.72)	1.29 (0.90–1.85)	1.86 (0.95–3.65)
86–89%	521	1.43 (0.91–2.26)	1.53 (1.06–2.21)	2.00 (1.01–3.94)
63–85%	445	1.74 (1.10–2.74)	1.74 (1.20–2.53)	2.39 (1.22–4.70)
P for trend		0.02	0.003	0.02
Model 2 (adjusted for age, sex, BMI, ethanol intake, current smoking, exercise habit, and physical activity)				
3% ODI				
<5.0	1307	1.00	1.00	1.00
5.0–14.9	418	0.95 (0.67–1.35)	1.14 (0.85–1.53)	1.13 (0.71–1.79)
≥15.0	111	1.27 (0.72–2.23)	1.69 (1.03–2.76)	1.28 (0.59–2.79)
P for trend		0.52	0.04	0.49
4% ODI				
<5.0	1528	1.00	1.00	1.00
5.0–14.9	251	1.28 (0.86–1.90)	1.53 (1.10–2.14)	1.21 (0.71–2.05)
≥15.0	56	1.16 (0.58–2.35)	1.49 (0.79–2.82)	0.48 (0.13–1.78)
P for trend		0.41	0.03	0.57
Average oxygen saturation				
97.2–99.5%	443	1.00	1.00	1.00
96.6–97.2%	458	1.00 (0.63–1.59)	1.00 (0.98–2.05)	0.65 (0.32–1.34)
95.8–96.6%	468	1.32 (0.85–2.07)	1.42 (0.98–2.05)	1.26 (0.68–2.35)
88.5–95.8%	465	1.41 (0.89–2.23)	1.60 (1.09–2.37)	2.12 (1.15–3.91)
P for trend		0.08	0.004	<0.001
Minimum oxygen saturation				
93–98%	416	1.00	1.00	1.00
90–92%	452	1.00 (0.64–1.56)	1.18 (0.82–1.71)	1.65 (0.83–3.26)
86–89%	521	1.09 (0.69–1.72)	1.27 (0.87–1.85)	1.64 (0.82–3.30)
63–85%	445	1.23 (0.77–1.94)	1.40 (0.95–2.06)	1.93 (0.96–3.88)
P for trend		0.29	0.10	0.10

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; ODI, oxygen desaturation index.

HOMA-IR, Matsuda index, and HOMA-B were also associated with the average oxygen saturation during sleep (*P* for trend <0.001, <0.001, and 0.02, respectively). No significant interaction between sex and ODI was noted for glucose intolerance (*P* = 0.64), HOMA-IR (*P* = 0.58) or Matsuda index (*P* = 0.054). No interaction between BMI and ODI was observed either for glucose intolerance (*P* = 0.53), HOMA-IR (*P* = 0.35), or the Matsuda index (*P* = 0.24).

Given that central obesity is strongly associated with type 2 diabetes, sensitivity analyses were conducted using waist circumference as covariate as a substitute for BMI to account for confounding effects of obesity. The adjusted odds ratios for impaired fasting glucose, glucose intolerance, and diabetes were 1.40 (95% CI, 0.81–2.44), 1.82 (95% CI, 1.12–2.96), and 1.40 (95% CI, 0.65–3.00) respectively comparing those with moderate-to-severe SDB to those without SDB. Furthermore, the adjusted HOMA-IR was significantly higher (*P* for trend < 0.001) and Matsuda index was significantly lower (*P* for trend < 0.001) with increasing SDB severity. Analyses that included adjustments for waist circumference or BMI were materially indifferent. Because some participants had comorbidities that might affect nocturnal oxygen desaturation, we also performed sensitivity analyses excluding all subjects with a history of any cardiopulmonary disease. In the resulting subsample, the adjusted odds ratio of glucose intolerance for those with moderate-to-severe SDB ($ODI_{3\%} \geq 15.0$ events/h) was 1.70 (95% CI, 1.01–2.86) compared with those without SDB (*P* for trend = 0.047). Finally, compared with participants with an average oxygen saturation during sleep in the range of 97.2–99.5%, the adjusted odds ratios of glucose intolerance and diabetes were 1.51 (95% CI, 1.00–2.28) and 2.25 (95% CI, 1.18–4.31; *P* for trend < 0.001), respectively, in those with an average oxygen saturation in the range of 88.5–95.8%.

4. Discussion

The findings of the current study reveal an independent association between severity of sleep-related intermittent hypoxemia and glucose intolerance in a sample of Japanese men and women. An association between severity of intermittent hypoxemia and

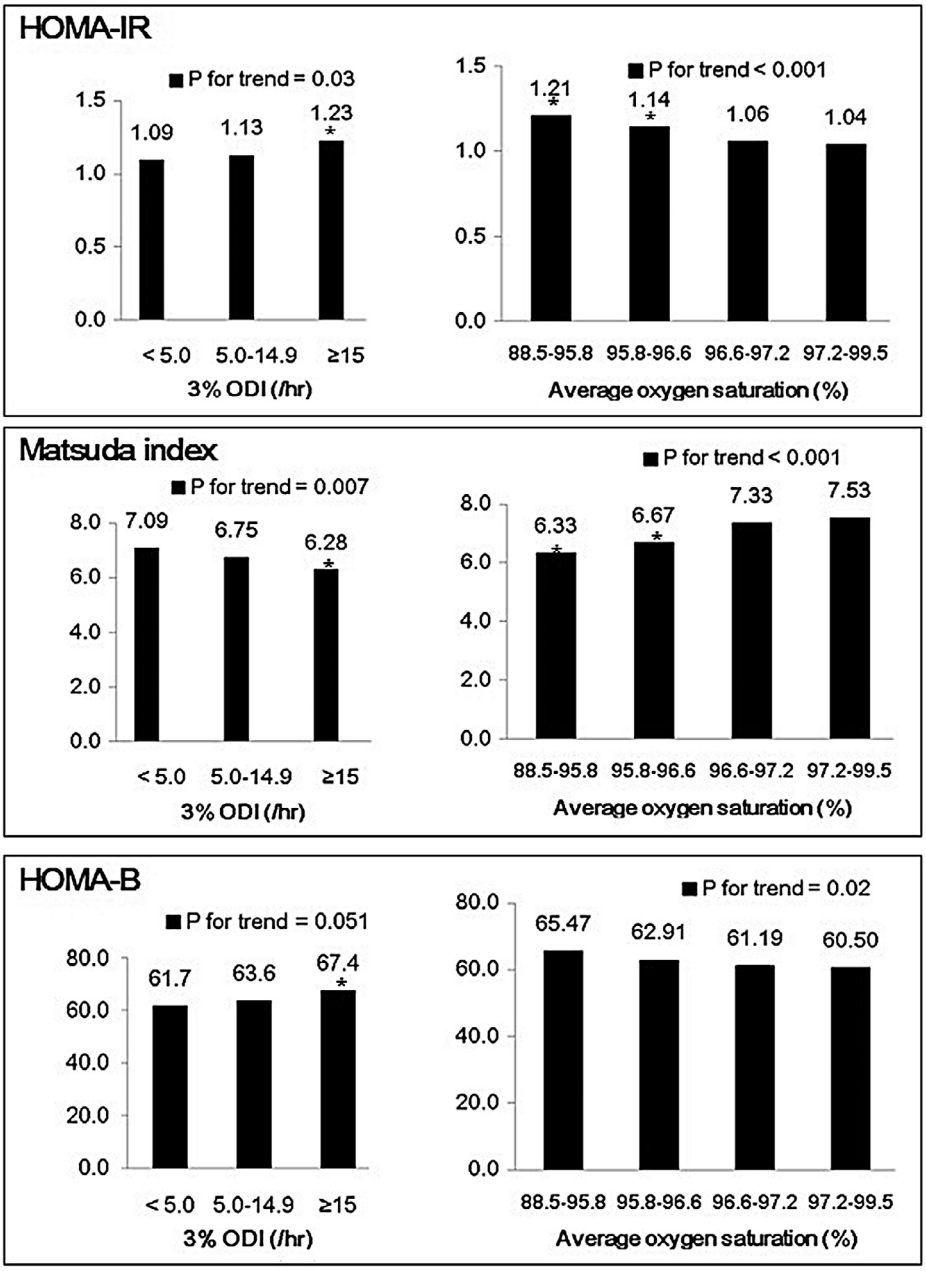

Fig. 1. Multivariable-adjusted mean values of HOMA-IR, Matsuda index, and HOMA-B. Adjusted for age, sex, body mass index, ethanol intake, current smoking, exercise habit, and physical activity. *$P < 0.05$ by analysis of covariance, compared with the lowest group. ODI, oxygen desaturation index; HOMA-IR/B, homeostasis model assessment of insulin resistance/beta-cell function.

insulin sensitivity was also noted with a higher ODI being independently correlated with lower insulin sensitivity. Moreover, there was also a robust association between average oxygen saturation during sleep and glucose intolerance. Finally, effect modification of the associations by sex or BMI was not observed.

The last decade has seen rapid progress in our understanding of the association between SDB and alterations in glucose metabolism. Several studies including the Wisconsin Sleep Cohort Study [2] and the Sleep Heart Health Study [3,16] have demonstrated that SDB is independently associated with abnormalities in glucose metabolism including insulin resistance, fasting and post-challenge hyperglycemia, and overt diabetes mellitus. Over the last few years, several prospective studies have suggested that SDB may, in fact, precede and lead to the development of type 2 diabetes [17–19]. In one of the most recent reports, longitudinal follow-up of 141 men without prevalent diabetes at baseline revealed that the adjusted odds ratio of developing diabetes is 4.4 (95% CI, 1.1–18.1) in men with an ODI ≥5.0 events/h [20] compared with those with an ODI < 5.0 events/h. Despite the consistency in the available evidence, the majority of published reports are based on Caucasian samples. Data on whether SDB and metabolic dysfunction are independently associated in large samples derived from the Asian continent are sparse [19,21,22]. Shin et al. showed that habitual snorers among 2719 non-obese Korean men had significantly higher blood glucose and insulin levels after a glucose load than non-habitual snorers [21]. Moreover, Muraki et al. demonstrated that intermittent hypoxemia during sleep was associated with the development of type 2 diabetes in 3864 Japanese men and women [19]. Finally, Lam et al. performed polysomnography on 165 Chinese outpatients with diabetes and found that OSA was more prevalent in

diabetes patients than in the general population [22]. The results of the present study add to the growing body of literature and indicate that SDB may be contributory, in part, to the emerging diabetes pandemic of diabetes in Eastern Asia.

Demonstrating an independent link between SDB, diminished insulin sensitivity, and a higher prevalence of glucose intolerance is not surprising. Exposure to intermittent hypoxia in various animal models has been shown to induce insulin resistance and alter pancreatic beta-cell function [4–6]. Data from human experiments indicate that healthy volunteers may develop insulin resistance even after a brief exposure (~5 h) to acute intermittent hypoxia [7]. The underlying mechanisms through which intermittent hypoxia in SDB may alter insulin and glucose homeostasis are not well defined. Several putative intermediate pathways could account for the observed association between sleep-related hypoxemia and impaired glucose metabolism as observed in the current study. First, it is well established that cyclical hypoxemia increases sympathetic nervous system activity during sleep and wakefulness [23]. The sympathetic nervous system has a fundamental role in the regulation of glucose and insulin homeostasis [24]. Increase in circulating catecholamines impairs insulin sensitivity [25], decreases insulin secretion [26], and reduces insulin-mediated glucose uptake [27]. Second, production of reactive oxygen species due to repetitive exposure to intermittent hypoxemia may inhibit insulin-stimulated glucose uptake in muscle and adipose tissue and damage the pancreatic beta-cell since it has relatively low levels of antioxidant enzymes [5,6]. Third, the chronic pro-inflammatory state in SDB, as evidenced by higher levels of C-reactive protein, interleukin-6, tumor necrosis factor-α, and circulating adhesion molecules may also predispose to the development of altered glucose metabolism in SDB [28]. Several lines of convergent evidence from experimental, clinical, and epidemiological studies suggest that pro-inflammatory cytokines may have a central role in regulating insulin action, and glucose homeostasis, and may increase the propensity for impaired glucose intolerance and type 2 diabetes [29]. However, the underlying mechanisms that govern the association between the inflammatory state and metabolic disturbance remain an area of active research.

A number of previous studies have reported an association between SDB and hepatic or peripheral insulin resistance [30–33]. The findings reported herein regarding the association of sleep-related intermittent hypoxemia with glucose intolerance, but not impaired fasting glucose, suggest that intermittent hypoxemia during sleep may have differential effects on hepatic and peripheral insulin sensitivity. It is well established that with impaired fasting glucose but normal glucose tolerance, hepatic insulin sensitivity is decreased whereas peripheral insulin sensitivity is preserved [34]. In contrast, glucose intolerance with normal fasting glucose is associated with normal or mildly reduced hepatic sensitivity, whereas peripheral insulin sensitivity is impaired moderately to severely [34]. Thus, the associations between $ODI_{3\%}$, average oxygen saturation during sleep, HOMA-IR (hepatic sensitivity) and the Matsuda index (hepatic and peripheral insulin sensitivity) indicate that sleep-related hypoxemia may have a greater impact on peripheral insulin than hepatic sensitivity, given that fasting hyperglycemia was not correlated with $ODI_{3\%}$. An important finding of our work is that the HOMA-B values increased according to SDB severity, suggesting a compensation in insulin secretion with increasing insulin resistance. Because treatment for diabetes was one of the exclusion criteria, participants with diabetes in the analysis sample were more likely to be in early stage of their disease process with preserved insulin secretion.

There are several limitations to the current study. First, home oximetry was used to quantify the severity of SDB. Whereas there is a strong correlation between the severity of SDB based on full-montage polysomnography and home oximetry, the lack of objective sleep measures limits our ability to examine the potential impact of SDB-related sleep fragmentation on glucose metabolism [35,36]. However, data from the Sleep Heart Health Study have shown that measures of sleep-related hypoxemia are significantly associated with glucose intolerance, whereas metrics such as arousal frequency are not [3]. Moreover, given that ODI and average oxygen saturation during sleep were associated with metrics of metabolic dysfunction in the current study, nocturnal hypoxemia is likely to be an important determinant of metabolic impairment. Second, because sleep duration on the night of home oximetry was based on self-report, there is inherent imprecision in quantifying the ODI given the lack of objective total sleep time. Third, because of our cross-sectional design, inferences regarding causal directions are not possible. There are also several major strengths in the current study. These include the large sample size, selection of a non-obese sample, inclusion of the OGTT to characterize metabolic dysfunction, and the careful consideration of numerous confounding covariates. Moreover, our study is the first report from Asia that used both objective measure of SDB and OGTT to evaluate the association between SDB and glucose metabolism in a large sample of community residents. Given that much of the evidence for association between SDB and altered glucose metabolism is based on Caucasian samples, the demonstration of an independent association in an Asian community-based cohort extends the generalizability of the notion that SDB is associated with adverse metabolic effects, and diminishes the likelihood that residual confounding can explain the observed association.

Funding sources

This study was supported in part by Grants-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology of Japan (Grants-in-Aid for Research B, No. 22390134 in 2010–2012 and No. 25293142 from 2013, Grand-in-Aid for Young Scientists B, No. 25860443 and No. 25860441 from 2013), Health and Labor Sciences Research Grants from the Ministry of Health, Welfare and Labor, Japan (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus, No. 201021038A in 2010–2012) and Grants-in-Aid for scientific research from The Ministry of Education, Culture, Sports, Science and Technology of Japan (Program for Enhancing Systematic Education in Graduate School in 2011). Dr Punjabi was supported by a National Institutes of Health Grant HL075078.

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.appet.2014.06.100.

Acknowledgement

The authors thank the staff and participants of the Toon Health Study for their valuable contributions.

References

[1] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–21.
[2] Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med 2005;172:1590–5.
[3] Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004;160:521–30.
[4] Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR, et al. Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol 2003;552:253–64.
[5] Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, et al. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 2007;175:851–7.

[6] Yokoe T, Alonso LC, Romano LC, Rosa TC, O'Doherty RM, Garcia-Ocana A, et al. Intermittent hypoxia reverses the diurnal glucose rhythm and causes pancreatic beta-cell replication in mice. J Physiol 2008;586:899–911.
[7] Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol 2009;106:1538–44.
[8] Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–904.
[9] Kumar GK, Rai V, Sharma SD, Ramakrishnan DP, Peng YJ, Souvannakitti D, et al. Chronic intermittent hypoxia induces hypoxia-evoked catecholamine efflux in adult rat adrenal medulla via oxidative stress. J Physiol 2006;575:229–39.
[10] Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006;29:1585–90.
[11] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.
[12] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–19.
[13] Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–70.
[14] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–7.
[15] Ishikawa-Takata K, Naito Y, Tanaka S, Ebine N, Tabata I. Use of doubly labeled water to validate a physical activity questionnaire developed for the Japanese population. J Epidemiol 2011;21:114–21.
[16] Seicean S, Kirchner HL, Gottlieb DJ, Punjabi NM, Resnick H, Sanders M, et al. Sleep-disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals: the Sleep Heart Health Study. Diabetes Care 2008;31:1001–6.
[17] Botros N, Concato J, Mohsenin B, Selim B, Doctor K, Yaggi K, et al. Obstructive sleep apnea as a risk factor for type II diabetes. Am J Med 2009;122:1122–7.
[18] Marshall NS, Wong KKH, Phillips CL, Liu PY, Knuiman MW, Grunstein RR. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med 2009;5:15–20.
[19] Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, et al. Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). Diabetologia 2010;53:481–8.
[20] Lindberg E, Theorell-Haglow J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and glucose metabolism – a long-term follow-up in a community-based sample. Chest 2012;142:935–42.
[21] Shin C, Kim J, Lee S, Shim J, In K, Kang K, et al. Association of habitual snoring with glucose and insulin metabolism in nonobese Korean adult men. Am J Respir Crit Care Med 2005;171:287–91.
[22] Lam DC, Lui MM, Lam JC, Ong LH, Lam KS, Ip MS. Prevalence and recognition of obstructive sleep apnea in Chinese patients with type 2 diabetes mellitus. Chest 2010;138:1101–7.
[23] Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep 2003;26:15–19.
[24] Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities – the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996;334:374–81.
[25] Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest 1980;65:717–21.
[26] Ahren B, Veith RC, Taborsky GJ Jr. Sympathetic nerve stimulation versus pancreatic norepinephrine infusion in the dog: 1). Effects on basal release of insulin and glucagon. Endocrinology 1987;121:323–31.
[27] Rizza RA, Cryer PE, Haymond MW, Gerich JE. Adrenergic mechanisms for the effects of epinephrine on glucose production and clearance in man. J Clin Invest 1980;65:682–9.
[28] Hatipoglu U, Rubinstein I. Inflammation and obstructive sleep apnea syndrome pathogenesis: a working hypothesis. Respiration 2003;70:665–71.
[29] Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006;17:4–12.
[30] Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165:670–6.
[31] Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165:677–82.
[32] Tassone F, Lanfranco F, Gianotti L, Pivetti S, Navone F, Rossetto R, et al. Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables. Clin Endocrinol (Oxf) 2003;59:374–9.
[33] Borel AL, Monneret D, Tamisier R, Baguet JP, Faure P, Levy P, et al. The severity of nocturnal hypoxia but not abdominal adiposity is associated with insulin resistance in non-obese men with sleep apnea. PLoS ONE 2013;8:e71000.
[34] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–9.
[35] Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A 2008;105:1044–9.
[36] Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest 2010;137:95–101.